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EDWARDS & ANGELL, LLP P.O. BOX 55874 BOSTON, MA 02205			BARNHART, LORA ELIZABETH	
			ART UNIT	PAPER NUMBER
			1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/713,678

Applicant(s)

WALSH, KENNETH

Examiner

Lora E. Barnhart

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-62 is/are pending in the application.
- 4a) Of the above claim(s) 1-29, 42-49 and 53-62 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 30-41 and 50-52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12/21/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Claims 1-62 are pending.

The examiner has determined that a new restriction requirement is necessary in this case. The following requirement for restriction and election of species should be substituted for the requirement mailed 8/11/05.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-20, 23-25, 28, 29, and 42-49, drawn to a method of promoting angiogenesis using statins and a protein, classified in class 585, subclass 400.
- II. Claims 1-18, 21, 22, 26, 27, and 42-49, drawn to a method of promoting angiogenesis using statins and a nucleic acid, classified in class 536, subclass 23.1.
- III. Claims 30-41 and 50-52, drawn to methods for activating an Akt polypeptide, classified in class 514, subclass 460.
- IV. Claims 53-62, drawn to a method for treating a wound, classified in class 514, subclass 460.

The inventions are distinct, each from the other because of the following reasons:

Groups I-IV are directed to methods that are distinct both physically and functionally, and are not required one for the other. The methods of Groups I and II do not share starting materials. The process steps of Groups I and III are similar to each other, but these methods do not share end points or starting materials (the cell of Group

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I must necessarily undergo angiogenesis, while the cell of Group III as claimed may be any cell). The method of Group IV does not share starting materials or process steps with any other Group. Therefore, a search and examination of all ~~six~~^{four} methods in one patent application would result in an undue burden, since the searches for the methods are not co-extensive, the classification is different, and the subject matter is divergent.

This application contains claims directed to the following patentably distinct species of the claimed invention: Conditions: (a) hypertension, (b) diabetic peripheral vascular disease, (c) gangrene, (d) Buerger's syndrome, (e) a wound, (f) ischemia of the muscle, (g) ischemia of the brain, (h) ischemia of the kidney, (i) ischemia of the lung, (k) ischemia of the heart, (l) ischemia of the limb, (m) severe occlusive vascular disease, (n) severe obstructive vascular disease, (o) peripheral vascular disease, (p) myocardial ischemia, (q) myocardial infarction, (r) coronary artery disease, (s) cerebral vascular disease, and (t) visceral vascular disease, as in claim 4, for example.

Statins: (u) lovastatin, (v) pravastatin, (w) simvastatin, (x) fluvastatin, (y) atorvastatin and (z) cerivastatin, as in claim 7, for example.

Mode of administration: (a') oral and (b') local, as in claims 8 and 9, for example.

Formulations: (c') salve, (d') gel, (e') film, and (f') patch, as in claim 15, for example.

Growth factors: (g') acidic fibroblast growth factors, (h') basic fibroblast growth factors, (i') vascular endothelial growth factor, (j') epidermal growth factor, (k') transforming growth factor- α , (l') transforming growth factor- β , (m') platelet-derived endothelial cell growth factor, (n') platelet-derived growth factor, (o') tumor necrosis

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factor- α , (p') hepatocyte growth factor, and (q') insulin like growth factor, as in claim 20, for example.

Akt proteins: (r') Akt-1, (s') Akt-2, and (t') Akt-3, as in claim 24, for example.

Downstream signaling events: (u') phosphorylation of an Akt substrate molecule, (v') a change in the rate of protein degradation, (w') a change in the level of mRNA transcription, (x') a change in the level of protein translation, (y') reduction of apoptosis, and (z') induction of angiogenesis, as in claim 34, for example.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

That is, if Group I is elected, applicant should also choose ONE condition from (a)-(t) above, ONE statin from (u)-(z) above, ONE mode of administration from (a') and (b') above, ONE formulation from (c')-(f') above, ONE growth factor from (g')-(q') above, and ONE Akt protein from (r')-(t') above.

If Group III is elected, applicant should also choose ONE statin from (u)-(z) above, ONE Akt protein from (r')-(t') above, and ONE downstream signaling event from (u')-(z') above.

If Group IV is elected, applicant should also choose ONE statin from (u)-(z) above and ONE Akt protein from (r')-(t') above.

If Group VI is elected, applicant should also choose ONE statin from (u)-(z) above and ONE formulation from (c')-(f') above.

Currently, claims 1, 3-49, and 53-62 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Melissa Hunter-Ensor on 2/2/06, a provisional election was made with traverse to prosecute the invention of Group III, claims 30-41 and 50-52. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-29, 42-29, and 53-62 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. During the same conversation, the species (w) simvastatin, (r') Akt-1, and (z')

induction of angiogenesis were also elected. Affirmation of this election must also be made by applicant in replying to this Office action.

Examination will commence at this time on claims 30-41 and 50-52 ONLY, as they pertain to the elected species as appropriate.

Information Disclosure Statement

Severals of the references cited on the information disclosure statement (IDS) submitted 12/21/04 were already submitted during the prosecution of parent case 09/590,740 (now U.S. Patent 6,689,807); these references have been annotated as such by the examiner. References AI-AO have not been considered, since these references are undated and unpublished (see 37 C.F.R. § 1.98 (b) (5)). Reference CA is a duplicate of reference C2 and has therefore not been considered.

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application No. 09/590740, filed 8/8/2000. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), **the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications.** If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within

the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or

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an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter, as it appears to have been in this case), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

It is noted that in a preliminary amendment filed 11/14/03, applicants inserted a line at the beginning of the specification claiming priority to 09/590,740. This sentence does not fulfill the requirements of the M.P.E.P. The first sentence in this case should point out that the instant case is either a continuation, a division, or a continuation-in-part of the parent case, and it should also point out the current status of the parent case, e.g. "This application is a division of U.S. Patent Application Serial Number 09/590,740, now U.S. Patent 6,689,807, which was filed June 8, 2000."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-41 and 50-52 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing phosphorylation of Akt in cultured mammalian cells comprising contacting said cells with particular amounts

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simvastatin, does not reasonably provide enablement for activating an Akt polypeptide in any other manner in any given cell using any given HMG CoA reductase inhibitor under conditions wherein said inhibitor activates the polypeptide. The specification does not define conditions under which every HMG CoA reductase inhibitor, known and unknown, would activate an Akt polypeptide in any way. The specification also does not reasonably provide enablement for detecting induction of angiogenesis in a cell culture environment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Claims 30-41 are broadly drawn to a method for activating an Akt polypeptide ("Akt") comprising contacting a cell containing said polypeptide with an HMG CoA reductase inhibitor (HCRI) under conditions wherein the HCRI activates Akt. Some dependent claims require an additional step in which Akt is detected or in which phosphorylation of Akt is detected. In some dependent claims, the HCRI is a statin

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selected from a list. The claims are also drawn to a method for determining whether a compound is an Akt-activating compound comprising determining Akt activation in the presence and absence of said compound, then comparing the results.

The method of claims 30-41 is broadly drawn to "activating an Akt polypeptide." According to a recent review by Scheid et al. (2003, *FEBS Letters* 546: 108-112; reference V), the mechanism of activation of Akt, which is also known as protein kinase B or PKB, is not fully elucidated (Abstract; page 108, column 1). Scheid et al. teach that Akt is regulated via phosphorylation at key serine and threonine residues by various kinases (page 109, column 1, through page 110, column 1), lipid binding at Akt's PH domain and control of subcellular localization (page 110, column 2), and possibly phosphorylation of tyrosine residues (page 111, columns 1 and 2). In short, according to Scheid et al., "[Akt] activation is complex...understanding of the precise molecular switches that must be flipped to achieve activation should lead to design of antagonists that are selective for this process" (page 111, column 2, and page 112, column 1). Clearly, even years after the time of the instant invention, skilled artisans have not reached consensus as to the full scope of processes that would result in "an activated Akt polypeptide." The examples in the specification center on studies of Akt phosphorylation in cultured cells; the specification provides no guidance for using HCRI to induce the changes in subcellular localization that Scheid et al. teach are key in the *in vivo* activation of Akt. Scheid et al. further teach that Akt activation has numerous cellular effects (Figure 1), but the specification provides evidence that only one activation event (phosphorylation of eNOS) occurs in the claimed method.

Furthermore, the method of claims 30-41 is claimed as being broadly applicable to "a cell containing an Akt polypeptide." The specification provides support only for contacting mammalian cells expressing Akt with HCRI, while the claims encompass all cells that contain any Akt polypeptide. The claims read on contacting an *E. coli* bacterial cell that recombinantly expresses a fragment of mouse Akt. Bacteria do not express Akt endogenously, nor do they express eNOS or the kinases taught by Scheid et al. to phosphorylate Akt. The person of ordinary skill in the art would therefore not have a reasonable expectation that a bacterial cell expressing recombinant Akt could be contacted with an HCRI in any amount, under any conditions, to produce activated Akt.

Furthermore, the method of claims 30-41 is drawn to the broad use of "an Akt polypeptide," a limitation that is not defined in the specification (see rejections below under section 112, second paragraph). According to Scheid et al., Akt comprises three domains (page 108, column 2) that are essential for its function and regulation. The specification provides no guidance for activating an Akt polypeptide that comprises, for example, only the C-terminal hydrophobic motif of Akt, no guidance for determining how this polypeptide could be activated, and no guidance for determining the extent of its activation.

Furthermore, the method of claims 30-41 requires contacting a cell comprising Akt with an HCRI "under conditions wherein the HCRI activates Akt." These conditions are simply not defined for every Akt in every cell for every HCRI. As discussed above, according to Scheid et al., the Akt activation art is unpredictable, and skilled artisans have failed to reach consensus as to the mechanisms of Akt activation even years after

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the time of the claimed invention. The specification provides no guidance for determining the conditions under which a given HCRI (including those known and those yet to be discovered) will activate Akt in any manner. Determining these conditions would require excessive experimentation on the part of the person of ordinary skill in the art.

Even if claims 30-41 are interpreted as being drawn to contacting a **mammalian** cell that comprises Akt with an HCRI, the specification as filed still fails to enable the skilled artisan to perform the claimed method with a reasonable expectation of success. The claims currently read on treating cells that are growing within a mammal, or treatment of an entire mammal; activation of Akt is an unpredictable art (see Scheid et al. and discussion above), so the person of ordinary skill in the art would not reasonably expect that a given administration of HCRI to a cell within a mammal's body would cause Akt activation. Indeed, Amaravadi et al. (2005, *Journal of Clinical Investigation* 115: 2618-2624; reference W) teach that even years after the instant invention, "therapeutics that directly target survival kinases [such as Akt] have not yet been developed for clinical use" (page 2618, column 1). Amaravadi et al. further discuss numerous obstacles to activating Akt in live patients (page 2622). In short, given the unpredictability of the art and the limited guidance by applicants, the person of ordinary skill in the art would not have a reasonable expectation of contacting a cell within a mammal with an HCRI to activate Akt.

Finally, applicants present a single working embodiment in which cultured human endothelial cells are incubated with 0.01-10mM simvastatin for an undisclosed time,

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after which the extent of phosphorylation of Akt1 at Ser⁴⁷³ was assessed (page 31, lines 28-31). No other type of Akt activation was investigated; no other HCRIIs were investigated. While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

Dependent claims 33 and 34 impose further limitations on the claims that are not enabled by the specification as filed; in light of the species election, claim 34 reads on a method comprising contacting a cell comprising Akt with an HCRI, then observing a downstream signaling event (for example, induction of angiogenesis) to detect activated Akt. First, the specification does not provide sufficient functional linkage between Akt activation and any downstream signaling event (including induction of angiogenesis) that the skilled artisan could interpret the signaling event as a direct indicator of Akt activation. In addition, angiogenesis is a complex process that requires the cooperation of at least several different cell types and several growth factors; the specification discloses only one experiment that involves angiogenesis (page 34, line 6, through page 35, line 3), in which rabbits with resected arteries were injected with simvastatin and observed for signs of revascularization; Akt activation was not directly assessed in this experiment.

The working examples provide no direct association between Akt activation and angiogenesis/vascularization. Applicant's experiments indicate two results that are not necessarily causally linked: (a) contacting cells with simvastatin in culture leads to phosphorylation of Akt, and (b) injection of simvastatin promotes revascularization at the capillary level in an animal model. There is no evidence in the specification or the art to suggest that angiogenesis is a direct indicator of Akt activation, as required in claim 34.

Dependent claim 36 imposes a limitation on the method that is not enabled by the specification as filed for all Akt polypeptides. Claim 36 requires that phosphorylation of Akt at two particular residues (Ser⁴⁷³ and Thr³⁰⁸) be an indicator of Akt activation; however, not all Akt sequences have these residues at these positions. A sequence comparison of human Akt1, Akt2, and Akt3; mouse Akt2; and *Drosophila* Akt1 (the sequences of which are publicly available from the NCBI database) indicates that Ser⁴⁷³ of human Akt1 corresponds to Ser⁴⁷⁴ of human Akt2, Ser⁴⁷² of human Akt3, Ser⁴⁷⁴ of mouse Akt2, and Ser⁵⁸⁶ of *Drosophila* Akt1. Similarly, Thr³⁰⁸ of human Akt1 corresponds to Thr³⁰⁹ of human Akt2, Thr³⁰⁷ of human Akt3, Thr³⁰⁷ of mouse Akt2, and Thr⁴²³ of *Drosophila* Akt1 (see reference U). The specification is not enabling for the limitation of claim 36 for any Akt that does not have a regulatory serine residue at position 473 and a regulatory threonine residue at position 308.

Dependent claims 40 and 41 impose limitations on the method that are not enabled by the specification as filed for all statins. While statins indeed are related in structure and function, their efficacy and activity varies. For example, according to Tornio et al. (2005, *Basic and Clinical Pharmacology and Toxicology* 97: 104-108;

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reference X), the statins and their lactones have varying ability to inhibit cytochrome P450 2C8 *in vitro* (Table 1; page 105, column 2). Simvastatin and lovastatin are the most potent CYP2C8 inhibitors, while rosuvastatin and pravastatin are not CYP2C8 inhibitors at all (Table 1). The statins also promote PAI-1 and t-PA expression *in vitro* to varying degrees (Wiesbauer et al., 2002, *British Journal of Pharmacology* 135: 284-292; reference U2), with pravastatin having no such activity at all (Table 2; page 286). The working examples in the specification indicate only that simvastatin causes phosphorylation of Akt *in vitro*; no indication is given as to the ability of the other statins (known and unknown) to do so. The person of ordinary skill in the art could not determine conditions wherein a particular statin (other than simvastatin) would cause Akt phosphorylation *in vitro* without extensive experimentation, given the unpredictable nature of statin activity.

The method of claims 50-52 is broadly drawn to "identifying an Akt-activating compound." As discussed above and in Scheid et al. (reference V), the mechanism of activation of Akt is not fully elucidated. Clearly, even years after the time of the instant invention, skilled artisans have not reached consensus as to the full scope of processes that would result in "an activated Akt polypeptide." The examples in the specification center on studies of Akt phosphorylation in cultured cells; the specification provides no guidance for using any compounds to induce the changes in subcellular localization that Scheid et al. teach are key in the *in vivo* activation of Akt. Scheid et al. further teach that Akt activation has numerous cellular effects (Figure 1), but the specification provides

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evidence that only one activation event (phosphorylation of eNOS) occurs in the claimed method.

Furthermore, the method of claims 50-52 is claimed as being broadly applicable to “a cell containing an Akt polypeptide.” As discussed at length above, the specification provides support only for contacting mammalian cells expressing Akt with HCRIs, while the claims encompass all cells that contain any Akt polypeptide.

Furthermore, as discussed at length above, the method of claims 50-52 is drawn to the broad use of “an Akt polypeptide,” a limitation that is not defined in the specification (see rejections below under section 112, second paragraph).

Furthermore, the method of claims 50-52 requires contacting a cell comprising Akt with an Akt-activating compound “under conditions wherein the Akt-activating compound activates Akt.” These conditions are simply not defined for every Akt in every cell for every possible compound. As discussed above, according to Scheid et al., the Akt activation art is unpredictable, and skilled artisans have failed to reach consensus as to the mechanisms of Akt activation even years after the time of the claimed invention. The specification provides no guidance for determining the conditions under which a given Akt-activating compound (including those known and those yet to be discovered) will activate Akt in any manner. Determining these conditions would require excessive experimentation on the part of the person of ordinary skill in the art.

Even if claims 50-52 are interpreted as being drawn to contacting **a mammalian** cell that comprises Akt with an Akt-activating compound, the specification as filed still

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fails to enable the skilled artisan to perform the claimed method with a reasonable expectation of success, as discussed at length above.

Finally, applicants present a single working embodiment in which cultured human endothelial cells are incubated with 0.01-10mM simvastatin for an undisclosed time, after which the extent of phosphorylation of Akt1 at Ser⁴⁷³ was assessed (page 31, lines 28-31). No other type of Akt activation was investigated; no other Akt-activating compounds were investigated. While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

In summary, the person of ordinary skill in the art would not have a reasonable expectation of success of practicing the claimed methods in their currently claimed scope, considering the unpredictable nature of the art and the limited direction provided in the specification. Applicant is urged to narrow the scope of the claim in terms of the Akt polypeptide, the type of cell, the HMG CoA reductase inhibitor (in claims 30-41 and 51), the Akt-activating compound (in claims 50 and 52), the mode of activation, and the method of detection.

Claims 30-39 and 51 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

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matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

M.P.E.P. § 2163 recites, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention... one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

The claims currently require contacting a cell containing Akt with "an HMG CoA reductase inhibitor." This limitation is functional, rather than structural, since the compound to be employed in the method is characterized by its activity against HMG CoA reductase. The specification does not provide an adequate link between the structure of an HCRI and its function of inhibiting HMG CoA reductase such that the person of ordinary skill in the art would immediately envisage every compound that meets this requirement.

M.P.E.P. §2163 recites, "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between

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function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus...when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. **For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus."**

While the statins are a class of small molecules that have been shown to inhibit HMG CoA reductase activity, they are not the only compounds that do so. HMG CoA reductase is inhibited when it is phosphorylated by AMP-dependent kinase (Hampton et al., 1996, *Trends in Biology* 21: 140-145; reference V2; see page 141, column 2). The specification defines HCRI as "a term of art which refers to a molecule which inhibits the enzymatic activity of the enzyme [HMG CoA reductase]" (page 5, lines 4-6). At no point, however, does the specification explicitly limit the interpretation of "HMG CoA reductase inhibitors" to "statins." AMP-dependent kinase is, therefore, an HCRI in accordance with the definition in the specification. According to Hampton et al., the regulation of HMG CoA reductase is complex (Abstract; page 141, column 1); the specification as filed provides no guidance by which the person of ordinary skill in the art could identify all compounds that inhibit HMG CoA reductase catalytic activity, including proteins and small molecules, without extensive experimentation.

For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession

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of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. The "written description" requirement may be satisfied by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that **fully set forth** the claimed invention. See *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and *Lockwood v. American Airlines, Inc.*, 107 F.3d at 1572, 41 USPQ2d at 1966. A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d at 1568, 43 USPQ2d at 1406 (Fed. Cir. 1997). See also *Fiers v. Ravel*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (Fed. Cir. 1993) (discussing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)).

An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In *University of Rochester*, the patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product. However, the patent did not disclose any compounds that could be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which

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peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that “[w]ithout such disclosure, the claimed methods cannot be said to have been described.”). See M.P.E.P. § 2163. In this case, the functional requirement that an HCRI “inhibit the enzymatic activity of the enzyme” (specification, page 5, line 5) and is “capable of activating Akt signaling in vascular endothelial cells” (*ibid.*, line 8) is not adequately linked to a particular structure, so the written description requirement has not been fulfilled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30-41 and 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is drawn to a method for “activating” an Akt polypeptide, but the nature of said activation is not particularly pointed out within the claim. It is not clear what properties an “activated Akt polypeptide” possesses that an “inactivated Akt polypeptide” does not. Clarification is required.

Claim 30 recites “an Akt polypeptide.” It is not clear whether this limitation refers to full-length Akt polypeptides or to any polypeptides that comprise any Akt domains or have any sequence similarity to Akt. It is not clear what properties of Akt an “Akt polypeptide” must possess. Clarification is required.

Claim 30 also recites the abbreviation “HMG CoA” without particularly defining the same within the claim. Clarification is required.

Because claims 31-41 depend from indefinite claim 30 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

It is not clear whether claim 31 further describes the contacting of claim 30 or whether this claim recites a contacting step that takes place in addition to that of claim 30. Clarification is required. If the former is the case, the examiner suggests the language "contacted with said HMG CoA reductase inhibitor *in vivo*."

Furthermore, the recitation of "*in vivo*" in claim 31 is queried; it is not clear, in light of the specification, whether "*in vivo*" refers to treatment of cells within a living organism or to living cells growing in a culture dish. Clarification is required.

Claim 33 recites the relative term "downstream" without providing a point of reference. Clarification is required.

Claim 36 refers to various amino acids that are to be phosphorylated, namely "Ser 473" and "Thr 308." These positions apparently correspond to the serine residue at position 473 and the threonine residue at position 308 in the amino acid sequence of human Akt1. Other human Akt polypeptides and Akt polypeptides from other species, however, do not have these residues at these positions. For example, Ser⁴⁷³ of human Akt1 corresponds to Ser⁴⁷⁴ of human Akt2, Ser⁴⁷² of human Akt3, Ser⁴⁷⁴ of mouse Akt2, and Ser⁵⁸⁶ of *Drosophila* Akt1. Similarly, Thr³⁰⁸ of human Akt1 corresponds to Thr³⁰⁹ of human Akt2, Thr³⁰⁷ of human Akt3, Thr³⁰⁷ of mouse Akt2, and Thr⁴²³ of *Drosophila* Akt1 (see reference U). The positions recited in claim 36 are undefined or incorrect for many Akt polypeptides. Clarification is required.

Claim 37 requires that the Akt polypeptide be expressed by an endothelial cell; it is not clear whether this claim is intended to further limit the cell of claim 30 (*i.e.*, “wherein the cell of claim 30 is an endothelial cell”) or whether the claim refers to a process in which Akt is expressed by an endothelial cell, extracted from an extract thereof, and somehow placed into a second cell, on which the method of claim 30 is performed. Clarification is required.

Claim 39 is confusing, because it does not particularly define the manner in which the Akt polypeptide relates to a polypeptide having a sequence identical to that in SEQ ID NO:1. Clarification is required. The examiner suggests the language “wherein the Akt polypeptide consists of a polypeptide having a sequence identical to that of SEQ ID NO:1.”

Claim 41 is confusing in that it recites numerous limitations within parentheses; it is not clear whether the matter in the parentheses is meant to be included in the claim. Clarification is required.

Claim 41 recites numerous trademarks. M.P.E.P. § 2173.05(u) recites, “It is important to recognize that a trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus a trademark or trade name does not identify or describe the goods associated with the trademark or trade name.” If the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. § 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982).

In order to avoid confusion, the examiner suggests the matter in parentheses in claim 41 be removed.

Claim 41 requires that “when the statin molecule is an inhibitor of HMG CoA, it is processed into the corresponding lactone form prior to local administration.” There are several problems with this language. First, statins are HMG CoA **reductase** inhibitors, not HMG CoA inhibitors *per se*; it is not clear how HMG CoA (3-hydroxy-3-methylglutaryl-coenzyme A; specification, page 2, line 6) could be inhibited. Second, the nature of the “correspondence” is not particularly pointed out. Third, the limitation “prior to local administration” lacks antecedent basis, since no other claims imply or recite a local administration step, merely a contacting steps. Finally, claim 41 depends from claim 40, which requires that the HMG CoA reductase inhibitor be a statin; it is not clear when a statin would not be considered an HMG CoA reductase inhibitor, as required by claim 41. Clarification on each of these points is required.

Claim 50 is drawn to a method for identifying an “Akt-activating” compound, but the nature of said activation is not particularly pointed out within the claim. It is not clear what properties an “Akt-activating compound” would impart to an Akt polypeptide. Similarly, claim 50 requires “determining the level of Akt polypeptide activation” without particularly pointing out the nature of said activation. Clarification is required.

Claim 50 recites “an Akt polypeptide.” It is not clear whether this limitation refers to full-length Akt polypeptides or to any polypeptides that comprise any Akt domains or have any sequence similarity to Akt. It is not clear what properties of Akt an “Akt polypeptide” must possess. Clarification is required.

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Because claims 51 and 52 depend from indefinite claim 50 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 51 recites the abbreviation "HMG CoA" without particularly defining the same within the claim. Clarification is required.

Claim 52 requires that the Akt polypeptide be expressed by an endothelial cell; it is not clear whether this claim is intended to further limit the cell of claim 50 (*i.e.*, "wherein the cell of claim 50 is an endothelial cell") or whether the claim refers to a process in which Akt is expressed by an endothelial cell, extracted from an extract thereof, and somehow placed into a second cell, on which the method of claim 50 is performed. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30, 31, and 37-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Hernandez-Perera et al. (1998, *Journal of Clinical Investigation* 10: 2711-2719; reference W2) taken in light of Kimura et al. (2000, *Biochemical and Biophysical Research Communications* 274: 736-740; reference X2) and Kureishi et al. (2000; *Nature Medicine* 6: 1004-1010; reference C2 on IDS). The claims are drawn to a

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method for activating Akt comprising contacting a cell that contains Akt with an HCRI under conditions wherein the HCRI activates Akt. In some dependent claims, the contacting occurs *in vivo*. In some dependent claims, the Akt is selected from a list. In some dependent claims, the HCRI is a statin, for example simvastatin.

Hernandez-Perera et al. teach contacting bovine aortic endothelial cells (BAEC) with 10 μ M simvastatin (page 2712, column 1; and Figure 1). Kimura et al. is cited solely as evidence that BAEC inherently express Akt (page 739, column 1). Kureishi et al. is cited solely as evidence that treating endothelial cells with 10 μ M simvastatin inherently promotes phosphorylation of Akt (Figure 1). The contacting of Hernandez-Perera et al. is conducted *in vivo* to the extent that the cells are alive (as opposed to an *in vitro* experiment, which might involve adding simvastatin to BAEC extract).

M.P.E.P. § 2112 reads, "The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." Something that is old does not become patentable upon the discovery of a new property, use, or application. In this case, applicant's discovery of a new function of the simvastatin treatment of Hernandez-Perera et al. (*i.e.*, promotion of Akt phosphorylation) does not in itself render the prior art method new.

The discovery of a new use for an old structure based on unknown properties of the structure *might* be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F.2d 1082,

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1090, 197 USPQ 601, 607 (CCPA 1978) and *In re Tomlinson*, 363 F.2d 928, 150 USPQ 623 (CCPA 1966). See M.P.E.P. § 2112.02.

Hernandez-Perera et al. teach contacting endothelial cells (which express Akt) with simvastatin. While Hernandez-Perera et al. do not teach subsequent activation of Akt, they do perform the same contacting step as in the present application. Because the method steps (*i.e.*, contacting Akt-containing cells with simvastatin) are the same, Hernandez-Perera et al. inherently teach the same process of Akt activation as in the current application. Hernandez-Perera et al. therefore anticipates the activation of Akt as instantly claimed.

In certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. *In re Wilson*, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism. Some specific examples in which later publications showing factual evidence can be cited include situations where the facts shown in the reference are evidence "that, as of an application's filing date, undue experimentation would have been required, *In re Corneil*, 347 F.2d 563, 568, 145 USPQ 702, 705 (CCPA 1965), or that a parameter absent from the claims was or was not critical, *In re Rainer*, 305 F.2d 505, 507 n.3, 134 USPQ 343, 345 n.3 (CCPA 1962), or that a statement in the specification was inaccurate, *In re Marzocchi*, 439 F.2d 220, 223 n.4, 169 USPQ 367, 370 n.4 (CCPA 1971), or that the invention was inoperative or lacked utility, *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974), or that a claim was indefinite, *In re Glass*, 492 F.2d 1228, 1232 n.6, 181 USPQ 31, 34 n.6 (CCPA

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1974), or that characteristics of prior art products were known, *In re Wilson*, 311 F.2d 266, 135 USPQ 442 (CCPA 1962)." *In re Koller*, 613 F.2d 819, 823 n.5, 204 USPQ 702, 706 n.5 (CCPA 1980) (quoting *In re Hogan*, 559 F.2d 595, 605 n.17, 194 USPQ 527, 537 n.17 (CCPA 1977) (emphasis in original)). However, it is impermissible to use a later factual reference to determine whether the application is enabled or described as required under 35 U.S.C. 112, first paragraph. *In re Koller*, 613 F.2d 819, 823 n. 5, 204 USPQ 702, 706 n.5 (CCPA 1980). See M.P.E.P. § 2124. In this case, the Kimura et al. and Kureishi et al. references were cited solely as evidence of inherent properties of BAEC and of simvastatin treatment, respectively, both of which are scientific truisms.

Claims 30-33, 35-40, and 50-52 are rejected under 35 U.S.C. 102(a) as being anticipated by Weiss et al. (1999, *Journal of the American Society of Nephrology* 10: 1880-1890; reference V3) taken in light of Kimura et al. (reference X2). The claims are drawn to a method for activating Akt comprising contacting a cell that contains Akt with an HCRI under conditions wherein the HCRI activates Akt. In some dependent claims, the contacting occurs *in vivo*. In some dependent claims, the method further comprises detecting activated Akt, for example detecting Akt phosphorylation, for example at threonine residue 308. In some dependent claims, the Akt is selected from a list. In some dependent claims, the HCRI is a statin.

Weiss et al. teach incubating rat vascular smooth muscle (VSM) cells with 100 μ M pravastatin for 1 hour, then lysing the cells and analyzing the phosphorylation of Akt at threonine 308 (Figures 4 and 5; page 1883, column 3, through page 1884, column 2;

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especially lanes 2 and 5 of Figure 5). Weiss et al. further teach incubating rat VSM cells in the presence and absence of pravastatin, then lysing the cells and analyzing the phosphorylation of Akt at threonine 308 (compare lanes 2 and 5 of Figure 5, in which the cells were treated with pravastatin, with lane 1 of Figure 5, in which the cells received no treatment). Weiss et al. teach that "pravastatin alone increased [phospho]Akt to a slight degree" (page 1884, column 2, line 1). Phosphorylation of Akt is considered a "downstream signaling event" in accordance with the specification, since it occurs downstream of the stimulation with pravastatin.

Kimura et al. is cited solely as evidence that BAEC inherently express Akt (page 739, column 1); thus, the methods of Weiss et al. read on the cited claims, since claims 37 and 52 do not require that the cells used in the method be endothelial cells, merely that the Akt be one that is expressed by endothelial cells.

Claims 50 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Burgering et al. (1995; *Nature* 376: 599-602; reference W3) taken in light of Kimura et al. (reference X2). The claims are drawn to a method for identifying an Akt-activating compound comprising contacting an Akt-containing cell with a compound under conditions wherein said compound activates Akt; determining the level of Akt polypeptide activation in the presence and absence of the compound; and comparing the two results. In some dependent claims, the Akt is expressed by endothelial cells.

Burgering et al. teach incubating fibroblasts in the presence and absence of various compounds (including PDGF, EGF, insulin, basic FGF, T-PA, and LPA) and

assaying the activity level of hemagglutinin-tagged Akt (Figure 1; page 599, columns 1 and 2). Burgering et al. further teach incubating fibroblasts in the presence and absence of PDGF and assaying the extent of phosphorylation of hemagglutinin-tagged Akt (Figure 3).

Kimura et al. is cited solely as evidence that BAEC inherently express Akt (page 739, column 1); thus, the methods of Burgering et al. read on the cited claims, since claim 52 does not require that the cells used in the method be endothelial cells, merely that the Akt be one that is expressed by endothelial cells.

Claims 50 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Alessi et al. (1996; *EMBO Journal* 15: 6541-6551; reference U3) taken in light of Kimura et al. (reference X2). The claims are drawn to a method for identifying an Akt-activating compound comprising contacting an Akt-containing cell with a compound under conditions wherein said compound activates Akt; determining the level of Akt polypeptide activation in the presence and absence of the compound; and comparing the two results. In some dependent claims, the Akt is expressed by endothelial cells.

Alessi et al. teach incubating L6 myotubes (which inherently express Akt) with and without wortmannin, then evaluating the degree of activation and phosphorylation of Akt (Figures 1 and 2; page 6542, column 1). Alessi et al. further teach incubating human embryonic kidney (HEK 293) cells that have been transfected with constructs encoding hemagglutinin-tagged Akt in the presence and absence of insulin and IGF-1, then

evaluating the degree of activation and phosphorylation of Akt (Figures 4 and 5; page 6543, column 1).

Kimura et al. is cited solely as evidence that BAEC inherently express Akt (page 739, column 1); thus, the methods of Alessi et al. read on the cited claims, since claim 52 does not require that the cells used in the method be endothelial cells, merely that the Akt be one that is expressed by endothelial cells.

No claims are allowed.

Applicant should specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lora E Barnhart



**IRENE MARY
PRIMARY EXAMINER**